## REMARKS

**The Election/Restriction Requirement:**

The Examiner indicated that the restriction requirement is stilled deemed proper and thus made it FINAL. Applicant has provisionally elected to prosecute Group V, claim 18 and still maintains its election with traverse.

**Rejection Under 35 U.S.C. §112, First Paragraph:**

The Examiner has rejected claim 18 under 35 U.S.C. §112 for failing to provide an enabling disclosure. The Examiner admits that the specification is enabling for a pharmaceutical composition of Serpens strain HBL-112, but asserts that the specification does not reasonably provide enablement for all pharmaceutical compositions of Serpens, immunologically active portions thereof, and antigenic epitopes cross-reactive with the Serpens genera. This rejection is respectfully traversed.

Citing Ellis, R.W., the Examiner asserts that "it is well recognized in the art that it is unclear whether a single protein derived from a pathogen will elicit protective immunity." (Office Action at page 3). The Examiner relies on a statement in Ellis, R.W. which provides, "[t]he key to the problem (of vaccine development) is the identification of that protein component of a virus or microbial pathogen that itself can elicit the production of protective antibodies... and thus protect the host against attack by the pathogen." (Office Action at page 3).

However, Applicant submits that the Examiner's reliance on Ellis is misguided because Ellis oversimplifies the art. Although it is true that some vaccines have been developed which meet Ellis' criteria, other vaccines are more complex, or approach immunity with different goals.

In this context, it is not necessarily a requirement that a vaccine elicit a "protective" immunity, but merely to induce resistance to microorganisms.

For example, Kilbourne, E.D. (U.S. Patent 4,029,763, "Description", fifth paragraph) teaches that a vaccine can be made which "allows the animal to become infected with the wild influenza virus with which it is challenged while protecting it against manifestations or symptoms of illness." Obviously, a vaccine which does not protect against infection (and, indeed, is not intended to protect against infection) is not operating through the "protective immunity" mechanism espoused by Ellis.

Also, Jawetz, et al. in "Review of Medical Microbiology", page 168, first complete paragraph (Appleton & Lange, Norwalk, 1987) describe five mechanisms by which antibodies may facilitate resistance to microorganisms: "antibodies (against antigens of microorganisms) may induce resistance because they (1) neutralize toxins or cellular products; (2) have direct bactericidal or lytic effect with complement; (3) block the infective ability of microorganisms or viruses; (4) agglutinate microorganisms making them more subject to phagocytosis; or (5) opsonize microorganisms".

Further, the Examiner omits a relevant portion of Ellis from his citation. The actual phrasing is: "The key to the problem is the identification of that protein component of a virus or microbial pathogen that itself can elicit the production of protective antibodies, **such antibodies having the capacity to neutralize infectivity** and thus protect the host against attack by the pathogen". (Emphasis added).

Thus, it is clear that Ellis is only discussing the development of vaccines with a blocking or "protective immunity" capacity - the third of the above five means by which antibodies are

known to induce resistance to microorganisms - and thus cannot be considered to be defining the art in this context.

To the contrary, because the role of a vaccine is to induce resistance to microorganisms, a vaccine which elicits antibody production in which antibodies act by any of the above mechanisms can be fairly claimed to be inducing resistance to that microorganism.

For example, Tizard (Tizard, I.R., In: "Veterinary Immunology" p. 21, first complete paragraph, W.B. Saunders Co., Philadelphia, 2000) states that "Antibodies, the major proteins of the immune system, are by far the most effective opsonins. They coat bacteria, link them to receptors on phagocytic cells, and provoke their ingestion."

Because opsonization is a process involving neutralization of bacterial zeta potential (and concomitant radius of shear reduction), and because phagocytosis can occur in the absence of antibody mediation "sometimes called nonimmune or surface phagocytosis" (see: Tortora, G.R., et al. Microbiology: an introduction, p.382, Benjamin/Cummings Publishing Co., Inc. Menlo Park), we can infer that any single antibody which binds to the microorganism - and by extension any binding monoclonal antibody population raised against a single epitope - serves to enhance resistance to that microorganism.

Indeed, the list by Jawetz itself is incomplete as it is also well known that antibodies can play a role in elicitation of an inflammation response (Terr, A.I., Mechanisms of Inflammation p.131, in: Basic and Clinical Immunology, Seventh Edition, Stites, D.P., Terr, A.I., Ed. Appleton & Lange, Norwalk).

In short, the Examiner's reference to a "single protein" does not address the entire scope of this application. In fact, an antibody response can be generated against all classes of organic compounds present in a microorganism including proteins, lipids, carbohydrate, nucleic acid, etc.

Furthermore, Tizard, I.R. (In: "Veterinary Immunology" p. 10, first paragraph) (W.B. Saunders Co., Philadelphia, 2000) notes that "most of the antigenicity of gram-negative bacteria is associated with the polysaccharide component (of the cell wall)" therefore the Examiner's emphasis upon protein structure appears inappropriately placed in the context of this application.

The Examiner's reliance on Fox (US Patent 4,879,213) is also misplaced. The Examiner cites Fox stating that "without knowing a protein's three dimensional structure there is no reliable method for determining which linear segments of the protein are accessible to the host's immune system" and also that "whether the three dimensional structure is known or not, short linear polypeptides often appear not to have the ability to mimic the required secondary and tertiary conformational structures to constitute appropriate immunogenic and antigenic determinants."

Again, as noted above, the relevance of the Examiner's reliance upon a protein-based epitope argument itself is questionable given that the more likely target is polysaccharide.

However, in cases where the target is a peptide, it is useful to note that Fox was filed in 1986. By 1994, the art had progressed considerably such that "cookbooks" had become available for such procedures that Fox considered problematic as seen in Wisdom, G.B. (Wisdom, G.B., Chapter 1, p.1 in: Peptide Antigens - A practical Approach. Wisdom, G.B., Ed., IRL Press, Oxford, 1994) who updates and corrects Fox when he states that "a major use of anti-peptide antibodies has been in the characterization of the cognate or parent protein" and that "relatively short, linear peptides can often induce useful cross-reactive antibodies".

Indeed, Pellequer states that "the most common method for detecting and localizing the putative gene product is to use antibodies raised against a synthetic peptide corresponding to an epitope of the putative protein, predicted on the basis of its primary structure." (Pellequer, J., et

al. Chapter 2, p.7, in: Peptide Antigens - A practical Approach. Wisdom, G.B., Ed., IRL Press, Oxford, 1994).

More particularly, the Examiner is placing the cart before the horse by insisting that the protein be defined in order to define the antibody when, in fact, the binding site, being complementary, means that the relevant epitope can be thoroughly described by the respective antibody as produced against Serpens. Returning once again to Wisdom (outside back cover in: Peptide Antigens - A practical Approach. Wisdom, G.B., Ed., IRL Press, Oxford, 1994) "anti-peptide antibodies are widely used in biochemistry and molecular biology for the measurement, location, and purification of specific oligopeptides."

Thus, the determination of immunologically active portions or antigenic epitopes cross-reactive with the Serpens genera is by no means unpredictable or requiring of undue experimentation. To the contrary, there are several reliable approaches available by which one skilled in the art and using antibodies raised against Serpens could obtain the claimed invention. For example, the "footprinting" method of Sheshberadaran and Payne (1989) (In: Methods in Enzymology, Ed. Lagone, J.J., Vol. 178, pp. 746-764, Academic Press, London).

Attention is particularly drawn to "Monoclonal Anti-idiotypic Antibody Vaccines against Poliovirus, Canine Parvovirus, and Rabies Virus" (Rimmelzwaan, G.F., et al., In: Methods in Enzymology, Ed. Lagone, J.J., Vol. 178, pp. 375-390, Academic Press, London). In this paper, the authors report on the routine preparation of numerous vaccines against specific epitopes as defined by the antibody raised against the initial antigen. "The binding of an antibody molecule to an epitope is mediated by the complementarity of the three-dimensional structures of the antigenic determinant and the antigen binding site of the antibody molecule. The conformation of the anti-idiotypic antibody (Ab2) binding to the paratope of Ab1 may therefore represent the

internal image of the epitope, and both can bind to the idiotype of the epitope-binding antibody. This constitutes the theoretical basis for the construction of idiotypic structures mimicking external antigen."

In making the rejection, the Examiner states the specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed". The Examiner also states that "[a]dequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The protein itself is required" and that "the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus" ... "the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus" and further, that "An adequate written description of a DNA... requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed invention." (Office Action at 4-5).

These Examiner's argument are misplaced. The present invention as set forth in the claims is not directed to a genus of nucleic acids or proteins per se, but rather the three dimensional structure or electron cloud ("epitope") which is defined by the corresponding antibody (Rimmelzwaan, G.F., supra). In the context of this application, therefore, what defines "an antigenic epitope cross-reactive with the Serpens genera" is the "internal image" established by the antibodies raised against members of the Serpens genera.

Because this epitope definition by an antibody is an extremely precise one, it therefore meets the requirements of the court for a "precise definition" by structure and physical property. A person of ordinary skill in the art would recognize that applicant has invented what is claimed.

The anti-Serpens antibodies are more than a simple reagent or "potential method" for isolation of what is claimed, they are in fact the very precise blueprint for what is claimed. Clearly, an enabling disclosure has been provided, and it is submitted that the rejection under 35 U.S.C. §112 be withdrawn.

**Rejection under 35 U.S.C. §102(b) Over Hespell:**

The Examiner has rejected claim 18 under 35 U.S.C. §102(b) as being anticipated by Hespell. This rejection is respectfully traversed.

The Examiner's assertion that Hespell discloses exactly the same pharmaceutical formulation is unfounded. Furthermore, the Examiner raised this identical objection in the underlying Patent 6,162,429 and his objections were previously overcome.

In addition, there is no question that Hespell never intended to formulate Serpens bacteria as a pharmaceutical composition. The organism was initially isolated from pond sediment and Hespell considered the bacteria to be an environmental organism. The Examiner acknowledges this fact but claims it is mooted by the priority of composition over use. This argument ignores the fact that invention can, and in this case does, indicate composition.

Water is a required component for life and must be considered ubiquitous in the investigation of biological processes. Keeton, W.T. (Biological Science, 3rd edition, p.41 "water", Norton, New York, 1980) states that "life as we know it on earth is totally dependent on water... Moreover, the chemical reactions that characterize life all take place in a water medium." Furthermore, Rodwell, V.W. ("Water" Chapter 2 p.7 in: Harper's Review of Biochemistry, 18th Edition, Martin, D.W., et al, Eds., Lange, Los Altos, 1981) states that "in living cells most biochemicals exist and most reactions occur in an aqueous environment. Water is an active

participant in many biochemical reactions and is an important determinant of the properties of macromolecules such as proteins."

Thus, if water is involved in all aspects of biological processes, then the presence or absence of water per se cannot be a reliable marker of pharmaceutical composition. Rather, water in a pharmaceutical composition must be a particular type of water.

Hespell initially isolated Serpens spp. from pond water. But Hickman, C.P., et al (Integrated Principles of Zoology, 6th ed., p.29, 4th complete paragraph, C.V. Mosby, St Louis, 1979) note that "surprisingly, lake water may contain a far higher organic content than does ocean water. Some organic substances found in water are organic phosphorus and organic nitrogen compounds, amino acids, carotenoid substances, and vitamins." Clearly, the presence of such contaminating compounds is inconceivable in a pharmaceutical composition and thus association of an organism with pond water cannot be considered as anticipating a pharmaceutical composition.

Similarly, the disclosure of Hespell of culturing the Serpens flexibilis in a lactate broth which contained 100 ml of distilled water as an ingredient of that broth cannot be seen to anticipate a pharmaceutical composition since none of the other ingredients were of pharmaceutical quality or functionality and thereby contaminate and are unacceptable for use in a pharmaceutical composition. Furthermore, Hespell never reported culturing, storing or handling of Serpens flexibilis in distilled water without other ingredients, thus in no way does Hespell anticipate any formulation envisioned by the present application.

Even if Hespell had disclosed the culturing of *Serpens flexibilis* in distilled water, it would still not anticipate the present invention since *Serpens flexibilis* "cultured" in distilled

water would necessarily be phenotypically distinct from *Serpens flexibilis* that would be used in a pharmaceutical composition by one trained in the art.

Finally, distilled water *per se* is simply not an acceptable pharmaceutical component, and thus could not be acceptable as an ingredient in a pharmaceutical composition. Distilled water is not of sufficient purity for use in a pharmaceutical composition and would be hypotonic with or without Serpens bacteria and thus represent a hazardous agent for use by injection. By way of further example, enclosed a copy of the relevant pages from the Sigma Chemical Company 2002-2003 "Biochemicals and Reagents for Life Science Research" catalog which lists 15 different types of water that are available for purchase. It should be noted that none of these 15 types of water is intended for use as part of a pharmaceutical composition.

It is therefore respectfully submitted the rejection under 35 U.S.C. §102(b) be withdrawn.

**Double Patenting:**

In response to the Examiner's non-statutory double patenting rejection, Applicant will submit a terminal disclaimer in compliance with 37 CFR 1.321, once the application is otherwise found to be in allowable condition.

Based on the foregoing remarks, Applicant respectfully submits that claim 18 is in condition for allowance and a timely Notice of Allowability is solicited. The undersigned attorney welcomes comments and suggestions from the Examiner. If a telephone conversation

can further prosecution of this case in any manner, the Examiner is urged to telephone the attorney at the number listed below.

Respectfully submitted,

SQUIRE, SANDERS & DEMPSEY L.L.P.

Dated: July 22, 2002 (Monday)

By: _____
Joseph Hyosuk Kim, Ph.D.
Reg. No. 41,425

801 S. Figueroa Street
14th Floor
Los Angeles, CA 90017-5554
(213) 689-6533

Enclosures: Kilbourne (USP 4,029,763); Jawetz et al. reference; Tizard et al. references; Tortora et al. reference; Stites et al. reference; Wisdom references; Langone references; Keeton reference; Martin et al. reference; Hickman et al. reference; Sigma reference.